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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,257	02/14/2002	Chih-Pin Liu	1954-313	5061

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EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,257	LIU ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-25,27-35 and 49-52* is/are pending in the application.

4a) Of the above claim(s) *6 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-25,27-35 and 49-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02032005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application claims the benefit of the filing date of provisional application 60/268,714.

Claims 5, 26 and 36-48 have been canceled.

New claims 49-52 have been added.

Claims 1-4,6-25,27-35 and 49-52 are currently pending.

Election/Restrictions

1. Applicant's election without traverse of the species of antigenic peptides related to diabetes in the reply filed on May 6, 2004 and confirmed in the reply filed August 16, 2004 is acknowledged.

Claims 6 and 7 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 6, 2004.

Claims 1-4, 8-25 and 26-35 and 49-52 are the subject of examination in the present Office Action.

2. **In view of Applicant's amendment filed February 3, 2005, only the following grounds of rejection are maintained.**

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-4, 8-12, 17-23, 27-29 and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Z'hu et al (Eur. J. Immunol. [1997] 27:1933-1941; U on form PTO-892 of record) in view of Chao et al (Immunogenetics [1997] 46:29-34; cited on form PTO-1449 filed June 18, 2002 of record).

It was previously stated: "Z'hu teaches a nucleic acid encoding a recombinant single-chain human MHC class II molecule (HLA-DR1) comprising an antigenic peptide covalently bound via a linker to the extracellular domain of the MHC class II beta chain. The linker allows the MHC class II molecule to properly fold and present the antigenic peptide (page 1934, second column in particular). Z'hu teaches that the nucleic acid encoding the beta chain and peptide was truncated to delete the transmembrane domain of the beta chain and attached to a nucleic acid encoding the extracellular domain of MHC class II alpha chain and then the insertion of a truncation signal to delete the transmembrane domain of the alpha chain (second column of page 1934, page 1935 and Figure 1 in particular).

Z'hu does not teach glutamic acid decarboxylase (GAD) peptides in association with MHC class II molecules.

Chao teaches the identification of peptide epitopes from GAD 65 that bind to a murine MHC class II haplotype that is associated with diabetogenesis in non-obese diabetic (NOD) mice (A^{g7}) (second column of page 29, Table 2 and Figure 2 in particular). Chao teaches that 63% of GAD reactive T cell hybridomas in the study reacted with peptide 206-220 of GAD 65, which is the same peptide as the instantly disclosed and claimed SEQ ID NO: 1 (column 1 of page 32, Table 2 and Figure 2 in particular). Chao further teaches that peptide 524-543 is a major immunogenic epitope of GAD 65 (Figure 3 in particular), which is the same peptide as the instantly disclosed and claimed SEQ ID NO: 2.

Chao teaches that the human MHC class II HLA-DRB1*0405 haplotype is a susceptibility allele for insulin-dependent diabetes mellitus (IDDM) and is structurally related to the murine A^{g7} haplotype of NOD mice (page 33, column 1 in particular). Chao teaches that SEQ ID NO: 1 does not completely fit the predicted motif for binding to HLA-DRB1*0405 or to A^{g7}. Chao teaches that this is not unusual, however, as predicted motifs are based upon peptide elution and therefore select for abundant peptides, which are not necessarily the most immunogenic peptides (page 33, column 1 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to use the guidance of the teachings of Z'hu to construct nucleic acid molecules encoding soluble single-chain MHC class II molecules of human HLA-DRB1*0405 covalently bound to the GAD 65 antigenic peptide of SEQ ID NO: 1. The artisan would have been motivated to combine the teachings with a reasonable expectation of success in order to examine the suggestion of Chao that HLA-DRB1*0405 may present the GAD 65 206-220 peptide to T cells in IDDM patients in light of the teaching of Z'hu that the unique properties of such engineered HLA molecules can facilitate an understanding of the nature of antigen recognition (Abstract in particular)."

Applicant's arguments filed February 3, 2005 have been fully considered but they are not persuasive.

Applicant argues that the combination of references does not render the claimed invention obvious because Chao does not teach that immunogenic peptides of GAD 65 bind to MHC class II and does not teach that recombinant molecules of the type claimed "should or could be made."

Applicant goes on to assert that Chao implies that "GAD 65 peptides presented by susceptible MHC class II alleles might not even exist." This last statement by Applicant is a piece-meal analysis of the teachings of Chao and will be addressed first.

What the reference actually states is:

> "[...] First, sequence studies by Ramansee and co-workers (1995) show that alleles which encode β chains lacking an aspartic acid at position 57 bind a subset of peptides with aspartic acid or glutamic acid at peptide position p9, which are not bound to any appreciable extent by alleles which encode β chains having an aspartic acid at position 57." [...]
>
> "Second, it has been reported that the susceptible or resistant *MHC* class II alleles plus peptide induce distinct kinds to [sic, read "of"] T-cell effector functions."
>
> "On the basis of these two clues, **it is likely that susceptible alleles (A^{g7}) predispose to IDDM by presenting a subset of peptides from islet cell autoantigens which are not presented effectively by diabetes resistant class II *MHC* alleles (A^{d}, $A^{g7.PD}$).** This subset of peptides, when bound to susceptible alleles, may induce a predominant Th1 T-cell response to islet cell autoantigens, which ultimately results in B-cell [sic, read "β"] destruction.
>
> [...] Some **immunodominant epitopes may be presented by both susceptible and resistant alleles. Nevertheless, the identification of GAD 65 peptides uniquely presented by the susceptible *MHC* class II alleles, if such exist**, would be a central finding in the unraveling the mechanism(s) by which *MHC* genes act to cause disease susceptibility." (Page 30, first column in particular; italics in original, bold emphases added for clarity)

Accordingly, Chao does not teach that diabetes-associated epitopes do not bind to susceptible alleles as asserted by Applicant. Rather, Chao teaches that some immunodominant alleles appear to be better presented by susceptibility alleles than by resistant alleles. Chao teaches that these same epitopes also may be bound by resistant alleles, but are not presented as efficiently by the resistant alleles as they are by the susceptible alleles. This is not a teaching away from Applicant's invention, nor is it a suggestion that the claimed complex could or should not be made as alleged by Applicant,

Applicant argues that Chao does not teach susceptibility alleles with immunogenic peptides, however Applicant is arguing a feature not recited in the claims. The argued feature is present only in newly introduced dependent claims that are not part of the instant ground of rejection, but are addressed *infra*.

Applicant further argues against the obviousness of the claimed invention based upon the declaration by Chih-Pin Liu filed on February 3, 2005 under 37 CFR § 1.132. the Liu declaration discloses that he was denied funding for a project regarding MHC class II tetramers because the reviewers doubted the tetramers could be made by the "proposed approaches." The Liu declaration further states that the Declarant believed that the rejection was a statement "that discovering peptides that bind to class II MHC molecules was unpredictable and risky" and cites Hackett (cited on form PTO-1449 filed February 3, 2005) to bolster this opinion. The Declarant goes on to assert that since the time of the

funding rejection, the Declarant has gone on to construct several MHC class II tetramers. The declaration and Applicant's arguments based thereupon are not found persuasive for several reasons.

First, the substance of the declaration is in regard to doubt on the part of the artisans reviewing the grant request on the ability of the Declarant to make MHC class II tetramers according to the "proposed approaches." The argued feature of "tetramers" is not part of any claim currently pending in the instant application. Accordingly, the declaration arguments are directed to a feature not claimed and are therefore off-point in regard to the rejection. If such tetramers are indeed what Applicant regards as the invention, perhaps Applicant should pursue claims to the tetramers in a subsequent filing.

Second, there is no assertion or evidence by the Declarant that the method used to successfully create MHC class II tetramers is the same as the "proposed approaches" rejected by the grant application reviewers. There is also no indication that either the rejected "proposed approaches" or the method successfully used to construct tetramers are the same as any method disclosed in the instant specification.

Third, based upon the Declarant's statements it is evident that the rejection of the grant proposal by the reviewers was due to doubt that the MHC class II tetramers could be made by the "proposed approaches," not a general statement by the reviewers and therefore artisans in general "that discovering peptides that bind to class II MHC molecules was unpredictable and risky."

Accordingly, the ground of rejection is maintained.

4. Claims 1-5, 8-13, 15, 17-24, 26-30, 32-35 and 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Z'hu et al (Eur. J. Immunol. [1997] 27:1933-1941; U on form PTO-892) in view of Chao et al (Immunogenetics [1997] 46:29-34; cited on form PTO-1449 filed June 18, 2002) and Crawford et al (Immunity [1998] 8:675-682; cited on form PTO-1449 filed June 18, 2002), all of record.

It was previously stated:: "Z'hu and Chao have been discussed supra.
The combined references do not teach labeling of the soluble MHC molecule with biotin.
Crawford teaches the biotinylation of soluble MHC class II molecules (see entire report, page 680, column 1 in particular). Crawford further teaches attachment of phycoerythrin/streptavidin complexes to the biotinylated soluble MHC class II/peptide complexes to create a stable multimeric molecular complex (page 680, column 1 in particular).
It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of Z'hu and Chao with the teachings of Crawford to create multimeric MHC class II complexes comprising GAD 65 peptide antigens. The artisan would have been motivated to combine the teachings with a reasonable expectation of success to create to create soluble single-chain MHC class II molecules of human HLA-DRB1*0405 covalently bound to GAD 65 antigenic peptides by combining the teachings of Z'hu and Chao as set forth supra and make stable multivalent complexes by way of biotinylation in the manner of Crawford because Crawford teaches that monomeric soluble MHC class II molecules have affinities too low for reliably detecting antigen-specific T cells,

while multimeric MHC class II complexes have increased avidity for T cells due to the cooperative effect of multipoint binding (page 679, column 1 in particular)."

Applicant argues that Crawford does not rectify the alleged deficiencies of Z'hu and Chao and does not provide motivation to combine the teachings of Z'hu with the teachings of Chao. The combination of Z'hu and Chao is discussed supra and Crawford is cited for the merits of its own teachings added to the previously combined teachings of Z'hu and Chao. Because Applicant has not made any further arguments specifically regarding the teachings of Crawford, this ground of rejection is maintained without further explanation.

5. Claims 1-5, 8-12, 14, 16-23, 25-29, 31, 35 and 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Z'hu et al (Eur. J. Immunol. [1997] 27:1933-1941; U on form PTO-892) in view of Chao et al (Immunogenetics [1997] 46:29-34; cited on form PTO-1449 filed June 18, 2002) and U.S. Patent No. 6,232,445 to Rhode et al (patent date May, 15, 2001, filed October 29, 1997; A on form PTO-892), all of record.

It was previously stated: "Z'hu and Chao have been discussed supra.
The combined references do not teach oligohistidine tags.
The '445 patent further teaches that recombinantly produced soluble MHC molecules can be engineered to comprises a tail or "tag," such as oligohistidine (6x-His) that can be used for purification [claims 9 and 10] (column 27, lines 8-20 and column 54, lines 59-64).
It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of Z'hu and Chao with the teachings of the '445 patent to create MHC class II complexes comprising GAD 65 peptide antigens and bearing an oligohistidine tag. The artisan would have been motivated to combine the teachings with a reasonable expectation of success to create to create soluble single-chain MHC class II molecules of human HLA-DRB1*0405 covalently bound to GAD 65 antigenic peptides by combining the teachings of Z'hu and Chao as set forth supra and tagging the molecules by incorporating an oligohistidine tail as taught by the '445 patent in order to simplify the purification of the recombinantly produced molecules from culture medium."

Applicant argues that Rhode does not rectify the alleged deficiencies of Z'hu and Chao and does not provide motivation to combine the teachings of Z'hu with the teachings of Chao. The combination of Z'hu and Chao is discussed supra and Rhode is cited for the merits of its own teachings added to the previously combined teachings of Z'hu and Chao. Because Applicant has not made any further arguments specifically regarding the teachings of Rhode, this ground of rejection is maintained without further explanation.

6. **The following NEW GROUNDS of rejection have been necessitated by Applicant's amendment.**

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 49-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Applicant has introduced new dependent claims that each recite a "Class II MHC molecule is an auto-immune disease-associated Class II MHC molecule." Applicant asserts that support for the recitation is found in paragraphs 5-7, 17 and 55. However, the cited passages of the specification disclose only a single mouse MHC class II molecule, I-A^{g7}, which is associated with the spontaneous development of diabetes in the NOD mouse when expressed on both MHC II alleles of the animal. The specification does not disclose any further examples in the mouse or human, nor does the term "disease-associated Class II MHC molecule" appear in association with the exemplified haplotype or elsewhere anywhere in the cited passages or in the specification or claims as originally filed as a whole. Accordingly, the term "disease-associated Class II MHC molecule" is not defined in the specification and constitutes new matter. Applicant is reminded that obviousness is not the standard for the addition new limitations to the disclosure as filed. Entitlement to a filing date does not extend to subject matter that is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Conclusion

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

F. Pierre VanderVegt, Ph.D.
Patent Examiner
April 19, 2005

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